ALKYL NITRILES TEST PLAN AND CATEGORY JUSTIFICATION

June 7, 2004 (Revised)

OVERVIEW

Eastman Chemical Company and Solutia Inc. jointly submit the following test plan and category justification for review under the Environmental Protection Agency's High Production Volume Chemical Challenge Program. The category consists of three alkyl nitriles – propionitrile, butyronitrile and isobutyronitrile.

The sponsors conclude that the category approach for these closely related substances is appropriate, and that the existing available data presented in the test plan meet the screening data needs for this category.

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1. Identification of Category Sponsors

The Alkyl Nitriles Category is being sponsored by Eastman Chemical Company and Solutia Inc.

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2. Introduction and Identification of Category Members

The EPA's "Chemical Categories" guidance sets forth a definition of what constitutes a "chemical category, for the purposes of the Challenge Program." Specifically, that definition states that a chemical category under the HPV Challenge Program "is a group of chemicals whose physicochemical and toxicological properties *are likely to* be similar *or* follow a regular pattern as a result of structural similarity." The Alkyl Nitriles Category has been selected with this guidance in mind.

The **category** consists of the following members:

1. Propionitrile (EINECS Propiononitrile), CAS No. 107-12-0, molecular structure: $CH_3CH_2C{\equiv}N$

2. Butyronitrile, CAS No. 109-74-0, molecular structure: $CH_3CH_2CH_2C{\equiv}N$

3. Isobutyronitrile (2-methylpropanenitrile), CAS No. 78-82-0, molecular structure: $(CH_3)_2CHC{\equiv}N$

The generic chemical structure of the category members and surrogates is depicted as:

$RC{\equiv}N$, where R = CH_3CH_2-, $CH_3CH_2CH_2$- or $(CH_3)_2CH$-

As can be seen from the molecular structures shown above as well as the generic chemical structure, all three category members have closely related structures and the same functionality. The category members differ in having either two or three carbons in the alkyl chain, and in the case of the butyronitrile and isobutyronitrile members the only difference is in their being isomers.

Given the same functionality and similar structure, one would expect much of the category behavior to be driven by the nitrile function. A putative metabolite of all three materials is cyanide (see section 3.4). As shown in the test plan below, symptoms of acute and repeated dose toxicity are similar to those of cyanide. In addition, the relatively short aliphatic hydrocarbon side chains and lack of functional groups that strongly promote hydrogen bonding is also expected to influence chemical physical and environmental fate properties in a similar manner. These properties will be compared and examined in the appropriate sections below.

Butyronitrile and isobutyronitrile are manufactured by one producer at one site (Eastman Chemical Company). Propionitrile is manufactured solely by Solutia Inc. at one site. All three category members are used as industrial chemicals, primarily as intermediates that are chemically converted to other chemicals. Although they are sold and shipped from the manufacturing sites to other manufacturing companies, these customers chemically convert them to other products or use them as industrial chemicals. There are no reported uses in consumer products or formulations. Any exposures to these chemicals are expected to occur primarily in the workplace. Propionitrile is used to make di-N-propylamine and pharmaceuticals, with reported uses as an industrial solvent and dielectric fluid (Lewis, 1997). Butyronitrile is used as a chemical intermediate for butyric acid, butyramide and pharmaceuticals and other organics, such as ketones and esters. Isobutyric acid is used to manufacture insecticides, as a catalyst in the polymerization of ethylene, and as a gasoline additive (Lewis, 1997)(Clayton, 1994).

Although these products are industrial chemicals with limited exposure potential, the sponsors are not making a claim for reduced testing. The sponsors believe that the existing data and category approach for these chemicals will address all required HPV Chemical screening endpoints.

3. Test Plan

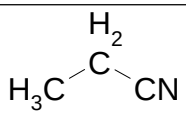
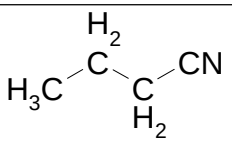
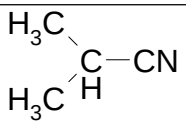
Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1). Studies receiving a Klimisch rating of 1 or 2 are considered to be adequate. Studies from other category members and surrogates were used to support studies assigned a reliability rating of 4 (not assignable).

Test Plan Matrix

The Alkyl Nitriles Category test plan matrix (as shown in Table 1) was constructed after a careful evaluation of all existing data (see Section 3 below). This matrix is arranged by category members (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries.

Table 1. Test Plan Matrix for Aliphatic Nitriles

Endpoint			
	Propionitrile 107-12-0	Butyronitrile 109-74-0	Isobutyronitrile 78-82-0
Physical-Chemical Data			
Melting Point	D	D	D
Boiling Point	D	D	D
Vapor Pressure	D	D	D
Partition Coefficient	D	D	D
Water Solubility	D	D	D
Environmental Fate Endpoints			
Photodegradation	E	E	E
Stability in Water*	E	E	E
Biodegradation	D	D	D
Fugacity	E	E	E
Ecotoxicity			
Acute Toxicity to Fish	D	D	D
Acute Toxicity to Aquatic Invertebrates	D	D	D
Toxicity to Aquatic Plants	C	D	D
Toxicological Data			
Acute Toxicity	D	D	D
Repeated Dose Toxicity	D	C	C
Genetic Toxicity – Mutation	D	D	D
Genetic Toxicity - Chromosomal Aberration	D	D	D
Reproductive Toxicity	D	C	C
Developmental Toxicity	D	D	D
Other Data			
Elimination (NR)	D	NR	NR
Mechanism of Toxicity (NR)	D	NR	NR

D = adequate experimental data; E = Endpoint fulfilled via estimation; T = endpoint to be filled by testing; C = endpoint fulfilled by other category members; NR = not required; *Estimate based on measured data for related material (acetonitrile) and analysis done by EPA personnel.

3.1 Chemical/Physical Properties

The results of chemical/physical property testing are shown in Table 2.

Table 2. Chemical/Physical Properties of Alkyl Nitriles

Chemical	Melting Point (°C)	Boiling Point[a] (°C)	Vapor Press.[b] (hPa)	Density (g/cm^3)	Water Sol.[b] (mg/l)	Log Kow[b]
Propionitrile CAS No. 107-12-0	-92.8[c]	97[c]	52[d]	0.7818[e]	93,380[f] 55,650[g]	0.16[h,i] 0.35[g]
Butyronitrile CAS No. 109-74-0	-112[e]	117.5[e]	26[j]	0.7954[e]	33,000[c] 27,840[g]	0.53[h] 0.837[g]
Isobutyronitrile CAS No. 78-82-0	-71.5[k]	103.8[k]	55.2[l]	0.77[m]	39,000[n] 32,500[g]	0.46[h] 0.76[g]

Refer to Section 2 of dossiers for additional information on category members.
[a] at 1013 or 1016 hPa; [b] at 20-25 °C; [c]Riddick et al. , 1986; [d]Solutia Inc., 2003; [e]Windholz et al. 1983; [f] Yaws, et al., 1992; [g] Estimated using EPIWIN [The EPI (Estimation Programs Interface) Suite™ developed by the Environmental Protection Agency Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC)(2000); [h] Sangster, 1989; [i] Temperature wasn't listed ; [j]Daubert and Danner 1989; [k]Weast, 1979; [l]Eastman Kodak Company, 1986a; [m] Eastman Chemical Company, 2002; [n] Unpublished study, Eastman Chemical Company, 2003.

3.1.1 Melting Point

Measured melting point data, which are available for all category members, indicate that these substances are all liquids with melting points well below -50°C.

3.1.2 Boiling Point

Measured boiling point data, which are available for all category members, indicate that these substances behave similarly, with boiling point ranges between 97 to 117.5 °C at atmospheric pressure.

3.1.3 Vapor Pressure

Consistent with their boiling points, category members have measured vapor pressures falling within a relatively close range of 26 to 55.2 hPa at 20-25°C.

3.1.4 Octanol/Water Partition Coefficient

The estimated octanol/water coefficients of category members fall within a range of 0.35 to 0.837. As one might expect, the log Pows increase somewhat going from propionitrile to the next higher homologs with higher molecular weights (butyronitrile and isobutyronitrile).

3.1.5 Water Solubility

Measured water solubility data are available for all category members. Solubility ranges from 33,000 mg/l for butyronitrile to 99,400 mg/l for propionitrile, the lowest homolog. Carbon branching appears to have little effect on water solubility (i.e. the solubility of isobutyronitrile was similar to straight chain butyronitrile).

3.1.6 Summary/Test Plan for Physical Properties

Measured data are available for melting point, boiling point, vapor pressure and water solubility for all category members. Estimated data for octanol/water partition coefficients are available. These data indicate that the category members behave similarly with respect to physical properties, and serve to support the category approach for these members. The members are all liquids with low melting points and boiling points that fall within a narrow range. Water solubilities range from slight to moderate. Partition coefficients are similar and are consistent with slight to moderate water solubility, and suggest limited potential to bioaccumulate. Existing data are sufficient to characterize physical property endpoints for these chemicals.

3.2 Environmental Fate/Pathways

As shown in Table 3 below, environmental fate parameters are consistent for category members.

Table 3. Environmental Fate Parameters for Alkyl Nitriles

Chemical	Henry's Law Constant (atm-m^3/mole)	Photodeg. OH radical rate constant (cm^3/molecule-sec) ($T_{1/2}$)	Predicted Environmental Distribution (Level III fugacity model)			
			Air (%)	Water (%)	Soil (%)	Sed. (%)
Propionitrile CAS No. 107-12-0	4.06E-5	0.194×10^{-12} 55.2 days	14.4	48.7	36.9	0.0821
Butyronitrile CAS No. 109-74-0	5.38E-5	0.498×10^{-12} 21.5 days	15	47.9	37	0.0821
Isobutyronitrile CAS No. 78-82-0	5.38E-5	0.703×10^{-12} 15.2 days	17.8	47.3	34.7	0.0809

All values are estimated from EPIWIN. Refer to Section 3 of repositories for additional information on category members.

3.2.1 Photodegradation

Photodegradation with hydroxyl radical sensitizer was estimated using EPIWIN/Aop (v1.90). Overall hydroxyl radical rate constants were calculated based on the summation of individual rate constants for each bond fragment in the molecule using the program algorithm. Estimated photodegradation hydroxyl radical rate constants range from 0.194 to 0.703 E-12 cm^3/molecule-sec. Calculated photodegradation half-lives for the three alkyl nitriles are in the range of 15.2 to 55.2 days, assuming a constant concentration of OH radical and pseudo first order kinetics.

3.2.2 Stability in Water

No hydrolysis studies were located for propionitrile, butyronitrile or isobutyronitrile, and EPIWIN Hydrowin cannot derive a water hydrolysis rate constant for nitriles. The theoretical hydrolysis of propionitrile and several other chemicals has been examined by Dr. Lee Wolfe at the USEPA Environmental Research Laboratory in Athens, Georgia. The results of these analyses were published in a report that could not be located by Dr. Wolfe. In a personal communication, Dr. Wolfe stated that propionitrile can hydrolyze (albeit slowly). According to a study cited in the Hazardous Substances Data Bank, the chemical hydrolysis of the related material acetonitrile in water is base-catalyzed (the rate constant for base catalyzed hydrolysis is 5.8X10-3/M-hr), but the half-life at pH 7 is more than 150,000 yrs (Ellington et al., 1988). Acetonitrile ($CH_3C{\equiv}N$)(CAS No. 75-05-8) is the 2-carbon analog of the category members, possessing the same functionality, but having one less carbon than propionitrile. Taken together, these data suggest that hydrolysis of propionitrile, butyronitrile or isobutyronitrile at environmentally relevant pHs will occur too slowly to be a significant means of degradation.

3.2.3 Fugacity

Level III fugacity data were calculated for category members using the EPIWIN program. Measured inputs to the program for each category member were the respective melting points, boiling points, vapor pressures and water solubilities presented in Table 2. The mass percentages are shown in Table 3. All three nitriles are predicted to partition mainly to water and soil (approximately 40 % in each compartment).

3.2.4 Biodegradation

As shown in Table 4 below, biodegradation data are available for all three nitriles.

Table 4. Comparison of Biodegradation Rates of Alkyl Nitriles

Category Member	Biodegradation Rate
Propionitrile CAS No. 107-12-0	40% biodegradable in 10 hours [a] Toxic to activated sludge at 500 mg/l [b]
Butyronitrile CAS No. 109-74-0	BOD5/COD ratio = 0.47 [c] 1.0 – 10.5 % of theoretical BOD at 500 mg/l [a]
Isobutyronitrile CAS No. 78-82-0	BOD5/COD ratio = 0.28 [d] BODs = 53.9 - 66.3% [e]

See Section 3.5 in dossiers for study details; [a]Symons et al., 1960; [b]Lutin, 1960; [c] Eastman Kodak, 1999a,b; [d] Eastman Kodak 1998b,c; [e] HSDB, 1999. Study was given a reliability rating of 4 because primary reference was not available.

Low concentrations of butryonitrile and isobutyronitrile (0.000195 – 0.000592 %) have been tested in BOD/COD studies similar to OECD TG-301C, Modified MITI Test (Eastman Kodak, 1998a,b). Both of these studies were given reliability ratings of 1 (valid without restriction). Results of these studies indicate that biodegradation of both materials occurred; however they were not readily biodegraded over a period of 5 days (both BOD5/COD ratios were < 0.5). Over a period of 20 days, the BODs for both of these materials increased (from 1.0 to 1.9 and 0.53 to 2.6, respectively), suggesting that the

materials can biodegrade over time. Results of a Japanese MITI test that was not available for review showed that a concentration of 100 ppm, isobutyronitrile was readily biodegraded over 14 days (BOD = 53.9 - 66.3%)(HSDB, 1999; Kitano, 1978; Sasaki, 1978). An additional test with results that could not be quantified showed that a mixed microbial culture that had been acclimated to organic cyanides and polychlorinated biphenyls could use propionitrile, n-butyronitrile and isobutyronitrile as a growth substrate (Chapatwala et al., 1992).

The ability of three different activated sludges to degrade propionitrile and butyronitrile has been tested using a Warburg respirator (Lutin, 1970). Results of these studies showed that over a period of 72 hours, a 500 mg/l concentration of butyronitrile was biodegraded to some extent (1.0 and 10.5% of theoretical BOD) by two of the sludges, but was toxic to another. At the same concentration, propionitrile was toxic to all three sludges. In contrast, an additional study employing a Warburg respirator and activated sludge showed that propionitrile (at a concentration of 1000 mg/l related to COD) was biodegraded by 40% after incubation for 10 hours (Symons et al., 1960). In this study, the kinetics of metabolism suggested that propionitrile was sequentially metabolized to propionamide and propionic acid.

3.2.5 Summary/Test Plan for Environmental Fate Parameters

Estimated values are available for the hydroxyl radical induced photolysis rate constant and atmospheric half-life, Henry's Law Constant, and Fugacity Level III environmental transport parameters. These data, which are summarized in Table 3, indicated that category members tend to partition to air, water and soil to a significant extent, and have limited retention in sediment. The Henry's Law Constants indicate that the substances will volatilize from the surface of water to the atmosphere, where they undergo hydroxyl radical induced photodegradation with a half-life of 15.2 to 55.2 days. The Kocs of propionitrile (8.3), butyronitrile (15.3), and isobutyronitrile (12.8) were estimated using the EPIWIN Pckoc Program. These low soil/sediment partition constants indicate that category members display high soil mobility, and can readily volatilize from soil surfaces or enter any adjoining aqueous environment.

Adequate biodegradation studies have been performed on all of the category members. The results suggest that the aliphatic nitriles are not readily biodegradable but will degrade over time, and that high concentrations may be toxic to microbes. The likelihood of obtaining environmentally relevant concentrations is low, based on use of this material as an industrial intermediate. No further testing is planned for any of the environmental fate endpoints.

3.3 Aquatic Toxicity

The acute toxicity of all three nitriles was measured in fish, invertebrates, and algae (with the exception of propionitrile, which has not been tested in algae). Results of the studies are summarized in Table 5.

Table 5. Comparative Aquatic Toxicity of Alkyl Nitriles

Chemical	**Fish LC_{50} (mg/l)[a]**	**Invertebrate EC_{50} (mg/l)[b]**	**Algae EC_{50} (mg/l)[c]**
Propionitrile CAS No. 107-12-0	1520 (fh minnow) [d] 41 (bluegill) 340 (trout)	250[e]	789[f]
Butyronitrile CAS No. 109-74-0	> 107 (fh minnow)	> 110	> 133.4 364.9 [e]
Isobutyronitrile CAS No. 78-82-0	> 102.1 (fh minnow)	> 94.3	> 87.8 429.5 [f]

LC_{50} = lethal concentration in 50% of organisms, EC_{50} = concentration required for 50% inhibition of growth, fh= fathead. See Section 4 of dossiers for details.
[a] Static, 96 hours (unless listed otherwise); [b] Static, Daphnia magna (48 hrs); [c] 72 hours; [d] Flow through study; [e] LC50; [f] estimated using EPIWIN/ECOSAR.

3.3.1 Acute Toxicity to Fish

The toxicity of propionitrile has been tested in fathead minnows in a flow through study (Geiger et al., 1990) and in bluegill sunfish and rainbow trout in static studies (ABC Laboratories Inc., 1981a,b). The 96-hour LC50 values (with confidence limits) for the respective species were 1520 (1450-1580) mg/l (measured concentration), 41 (28-66) mg/l (nominal concentration), and 340 (180-560) mg/l (nominal concentration). Reliability ratings of 2 (valid with restrictions) were assigned to the static studies since concentrations of material were not analytically confirmed. A rating of 1 was assigned to the flow through study, since it was comparable to a guideline study.

The toxicity of n-butyronitrile and isobutyronitrile to *Pimephales promelas* (fathead minnow) was tested in static, 96-hour limit studies which conformed to OECD test guideline 203 and were given reliability ratings of 1 (valid without restriction)(Eastman Kodak, 1998d; 1999c). Nominal concentrations of 120 mg/l were tested in both studies. The analytically measured concentrations of n-butyronitrile and isobutyronitrile in the studies were 107 and 102.1 mg/l, respectively. In both studies, none of the exposed fish died or exhibited abnormal behavior. Therefore, 107 and 102.1 mg/l were considered to be the no observable effect concentrations (NOECs) for n-butyronitrile and isobutyronitrile, respectively.

3.3.2 Acute Toxicity to Aquatic Invertebrates

A static, 48-hour toxicity test to *Daphnia magna* has been performed with propionitrile (ABC Laboratories, Inc., 1981c). The 48-hour LC_{50} value (with confidence limits) was 250 (210-290) mg/l (nominal concentration). A reliability rating of 2 (valid with restrictions) was assigned since concentrations of material were not analytically confirmed.

The toxicities of n-butyronitrile and isobutyronitrile to *Daphnia magna* were tested in static, 48-hour limit studies which conformed to OECD test guideline 202 and were given reliability ratings of 1 (valid without restriction) (Eastman Kodak, 1998e, 1999d). Nominal concentrations of 120 mg/l were tested in both studies. The analytically measured concentrations of n-butyronitrile and isobutyronitrile in the

studies were 110 and 94.3 mg/l, respectively. No abnormal behavior or immobility was observed in daphnia treated with 94.3 mg/l isobutyronitrile; therefore, this concentration was the NOEC. In the study with n- butyronitrile, 1/20 daphnids was observed to be immobile at 48 hours. This was not considered to be related to treatment, since the incidence was < 10%. Therefore, 100 mg/l was the NOEC for n-butyronitrile. According to the EPA's assessment criteria, the LC50 values correspond to a "low concern level".

3.3.3 Acute Toxicity to Aquatic Plants

The toxicity of n-butyronitrile and isobutyronitrile to *Selenastrum capricornutum* was tested in 72-hour limit studies, which conformed to OECD test guideline 201 and were given reliability ratings of 1 (valid without restriction) (Eastman Kodak, 1999e, 2000). Nominal concentrations of 200 mg/l were tested in both studies. The analytically measured concentrations of n-butyronitrile and isobutyronitrile were 133.4 and 87.8 mg/l (mean), respectively. There was no effect of treatment on growth rate or biomass; therefore, the EC_{50} values were higher than the concentrations that were tested. Both of these concentrations are within an order of magnitude of the EC_{50} concentrations calculated by ECOSAR for these materials (364.9 and 429.5 mg/l, respectively). ECOSAR is an appropriate model to estimate toxicity to algae since the mechanism of toxicity to fish (interruption of cellular utilization of oxygen by cyanide) is not relevant for plants. Since the ECOSAR value estimated for propionitrile is greater than these values, it is expected that the experimental EC_{50} concentration for propionitrile toxicity to algae is at least 87.8 mg/l, which is the experimental value for the nitrile with the lowest ECOSAR-estimated value.

3.3.4 Summary/Test Plan for Ecotoxicity

In conclusion, adequate tests exist for all three nitriles in all three of the required species (with the exception of priopionitrile toxicity to algae). Algal toxicity data for n-butyronitrile and isobutyronitrile (which are similar), along with the EPIWIN estimate for propionitrile toxicity to algae are sufficient to fill the algal toxicity endpoint for propionitrile. The fact that the EC_{50} values estimated by ECOSAR for n-butyronitrile and isobutyronitrile toxicity to algae are within an order of magnitude of experimental values for these materials lends support to this approach. No further testing is necessary.

3.4 Mammalian Toxicity

3.4.1 Acute

Acute toxicity data for the category members are summarized in Table 6. The oral and inhalation LD_{50} values of propionitrile, n-butyronitrile and isobutyronitrile in rats are similar. The oral LD_{50} values in rats for all three nitriles are within the range of 40 – 270 mg/kg (Younger Laboratories Incorporated, 1979, 1980; Eastman Kodak, 1957, 1960, 1961; Smyth et al., 1962). Inhalation LD_{50} values (for 1 or 4 hours of exposure) are from > 1000 to 1465 ppm (Younger Laboratories Incorporated, 1978, Eastman Kodak, 1986b,c,d). Whereas the dermal LD_{50} values of n-butyronitrile and isobutyronitrile in rabbits are similar (389 and 239 mg/kg, respectively), the dermal LD_{50} value of propionitrile in rabbits is lower (40-90 mg/kg depending on purity)(Smyth et al., 1962; Biodynamics Inc., 1981a,b,c).

Table 6. Acute Mammalian Toxicity of Alkyl Nitriles

Category member	Acute Rat Oral LD_{50} (mg/kg)	Acute Rat Inhalation LC_{50} (ppm)	Acute Rabbit Dermal LD_{50} (mg/kg)
Propionitrile CAS No. 107-12-0	40 [a] 75 (M), 270 (F) [b]	1465 (4 hr LC50) [c]	40-90 [d]
Butyronitrile CAS No. 109-74-0	50-100 [e] 111 (male rat) [f]	1848 (1 hr LC10) [g] > 1147 (1 hr LC50) [h]	398 [f]
Isobutyronitrile CAS No. 78-82-0	77 (male rat) [f] 50 [i] 50-100 [j]	1173 (1 hr LC10) [k] > 1000 (1 hr LC50) [l]	239 [f]

LD_{50} = lethal dose in 50% of animals (male and female unless listed otherwise); LC_{50} = 4 hour lethal conc. in 50% of rats (unless listed otherwise). Study details are found in the dossiers (Section 5.1)
[a] Younger Laboratories Inc., 1980; [b] Younger Laboratories Inc., 1979; [c] Younger Laboratories Inc., 1978;
[d] Biodynamics Inc. 1981a,b,c; [e] Eastman Kodak, 1960; [f] Smyth, 1960; [g] Eastman Kodak, 1987; [h] Eastman Kodak, 1986b; [i] Eastman Kodak, 1961; [j] Eastman Kodak, 1957; [k] Eastman Kodak, 1986c; [l] Eastman Kodak, 1986d;

Johnannsen and Leviskas have hypothesized that the acute toxicity of nitriles is due to release of cyanide upon metabolism (Johannsen and Leviskas, 1986). These investigators cite several different findings that support this hypothesis. First, the signs of acute nitrile intoxication (dyspnea, gasping, ataxia, and convulsions) are similar to those seen after acute cyanide poisoning. Second, the time course lasts several hours, suggesting that these agents require metabolism by the liver to be toxic. Third, cyanide and thiocyanate have been found in urine and blood after exposure to aliphatic nitriles. In support of this hypothesis, Willhite and Smith (1981) have shown that the acute toxicities of aliphatic nitriles (including propionitrile and butyronitrile) and formation of thiocyanate in mice are inhibited by antagonists of inorganic cyanide (sodium thiosulfate and sodium nitrite) and a hepatotoxicant (carbon tetrachloride). This study is summarized robustly in the dossiers for propionitrile and butyronitrile, and unequivocally shows that these two materials cause acute toxicity by the same mechanism. Since the symptoms of acute toxicity of isobutyronitrile are identical to those of n-butyronitrile and propionitrile, it is likely that this material also produces acute toxicity through liberation of cyanide.

In conclusion, adequate acute toxicity studies have been performed on all three nitriles in the category. Results of acute toxicity studies with propionitrile, n-butyronitrile and isobutyronitrile are remarkably similar (with the possible exception of priopionitrile, which is more potent by the dermal route).

3.4.3 Repeated Dose

The repeated dose toxicity of butyronitrile and isobutyronitrile have not been tested. The effect of inhalation of 60, 120 or 209 ppm propionitrile, 6 hr/day, 5 days/week over 14 weeks was tested in Sprague Dawley rats (Velasquez and Thake, 1984). A NOAEL was not established in this study, as all concentrations tested were toxic. Symptoms of neurotoxicity (ataxia, tremors and convulsions) were noted at the highest concentration tested. Labored breathing, nasal and ocular discharge, salivation, hypoactivity and/or alopecia were observed in all exposed groups. In addition, all groups had

significant decreases in red blood cells and hemoglobin values and increases in urine thiocyanate concentrations (a marker for cyanide toxicity) and spleen weights. No histopathological changes were noted in any of the organs (with the exception of hemosiderin deposits in the spleens of 11/15 females exposed to 120 ppm).

In general, symptoms of toxicity in this study are consistent with the rapid elimination of propionitrile after inhalation exposure (Biodynamics Inc, 1981d, 1987) and results of acute inhalation toxicity studies with propionitrile, n-butyronitrile and isobutyronitrile. The additional finding of toxicity to red blood cells and the spleen at a concentration that does not produce other symptoms of toxicity also is in agreement with the hypothesis that the toxicity of the nitriles is mediated through cyanide (Willhite and Smith, 1981). Heme in the hemoglobin of red blood cells avidly binds cyanide; therefore, red blood cells are targets of cyanide toxicity. Since the acute toxicity profiles of propionitrile, n-butyronitrile and isobutyronitrile are similar, the repeated dose toxicity profiles at similar concentrations of these materials should also be similar. Therefore, repeated dose toxicity testing of n-butyronitrile and isobutyronitrile is not necessary.

3.4.4 Genetic Toxicity

The genetic toxicity of the alkyl nitriles is summarized in Table 7.

Table 7. Genetic Toxicity of Alkyl Nitriles

Category Member	**Ames Test (w/wout activation)**	**Mammalian Cell Mutagenesis[a]**	**In vitro Cytogenicity[b]**	**In vivo Cytogenicity[c]**
Propionitrile CAS No. 107-12-0	Negative[d]	Negative	No data	Negative
Butyronitrile CAS No. 109-74-0	Negative	No data	Negative	No data
Isobutyronitrile CAS No. 78-82-0	Negative	No data	Negative	No data

Study details are located in the dossiers (Sections 5.5 and 5.6). [a] mouse lymphoma cell assay; [b] Chinese Hamster Ovary Cell ; [c] mouse bone marrow cells; [d] Study was given a reliability rating of 4

3.4.4.1 Mutagenicity

Propionitrile tested negative at concentration of up to 10,000 micrograms/ml in an Ames test conducted with *S. typhimurium* strains TA98, TA100, TA1535, and TA1538 (Flowers, 1977). This test was given a reliability rating of 4 (and therefore is not adequate), due to limited documentation and other inadequacies.

The results of a well-conducted mammalian cell mutagenicity study with a commercial material containing 97.8% propionitrile, 0.3% adiponitrile, 0.1% paranitrosophenylamine, 0.1% water and

<0.1% acrylonitrile or solids, in cultured mouse lymphoma L5178Y cells were negative (Microbiological Associates, 1982). Concentrations of up to 5000 micrograms/plate n-butyronitrile and isobutyronitrile were tested for mutagenicity in EEC Guideline bacterial mutagenicity studies conducted with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and E. coli strain WP2uvra- in the presence and absence of metabolic activation (Covance Laboratories Inc, 1999a,c). The results of these tests were negative.

3.4.4.2 Chromosomal aberration

In vitro

n-Butyronitrile and isobutyronitrile have been tested for the ability to cause chromosomal aberrations in an OECD Test Guideline 473 study performed with cultured Chinese Hamster Ovary Cells (CHO WBL line) (Covance Laboratories Inc., 1999c,d). In both studies, there was no significant effect of the test material on the number of cells with aberrations (with and without metabolic activation). In the tests with n-butyronitrile and isobutyronitrile, the highest concentrations of test material used (701 and 700 micrograms/ml, respectively) did not cause a significant reduction in the mitotic index. Higher concentrations were not tested because 700 micrograms/ml was the highest recommended concentration for the assay.

In vivo

The ability of propionitrile (100 or 200 mg/kg orally) to cause chromosomal aberrations in bone marrow cells was tested in Sprague-Dawley rats (Hazleton Biotechnologies Corporation, 1985). There was no effect of treatment on the frequency of chromosomal aberrations, mean chromosome number or mitotic index. The study was conducted according to GLP, but was given a reliability rating of 2 (valid with restrictions) since only 2 animals were available for analysis at 200 mg/kg.

In conclusion, adequate studies have been performed which show that the nitriles are not genotoxic. The results of studies with propionitrile indicate that small amounts of contaminants present in commercial preparations of this material may be mutagenic.

3.4.5 Reproductive and Developmental Toxicity

3.4.5.1 Reproductive Toxicity

Reproductive toxicity tests with n-butyronitrile or isobutyronitrile have not been performed. The effect of propionitrile on female and male fertility was tested in two separate studies that were given reliability ratings of 1 (valid without restriction)(Kier, 1984a,b). In the female fertility study, up to 210 ppm propionitrile was administered by inhalation, 6 hrs/day, 7 days/week, to females only, 21 days prior to mating and during mating until copulation was confirmed. For the study in males, up to 200 ppm propionitrile was given to males only by inhalation, 6 hours/day, 5 days a week, for 57 days (46 days prior to mating and 11 days during mating). In either study, there was no effect of propionitrile on fertility. In both studies, signs of acute cyanide toxicity (arched back, hypoactivity, salivation, lacrimation and/or labored breathing) were observed in high and mid dose animals. Signs of toxicity generally abated by the morning after exposure.

The signs of toxicity observed in this study are consistent with those observed in the repeated dose study with propionitrile and acute toxicity studies with all three nitriles. Furthermore, there were no effects on any reproductive organ examined in the repeated dose propionitrile study. Since the category members have similar structures, metabolism and acute toxicity profiles, it is expected that they would have a similar reproductive toxicity profile. Therefore, results of the fertility study with propionitrile should be predictive of those for n-butyronitrile and isobutyronitrile. No additional testing is necessary.

3.4.5.2 Developmental Toxicity

Results of developmental toxicity tests with the aliphatic nitriles are summarized in Table 8.

Table 8. Developmental Toxicity of Alkyl Nitriles

Category Member	Animal	Treatment	Effects
Propionitrile CAS No. 107-12-0	Sprague-Dawley rat	Gavage, 20, 40, 80 mg/kg/day, GD 6-19	NOAEL (maternal) = 40 mg/kg/day NOAEL (teratogenicity) = 80 mg/kg/day NOAEL (fetotoxicity) = 40 mg/kg/day. Decreased fetal body weight and increased skeletal variants at 80 mg/kg/day
Butyronitrile CAS No. 109-74-0	Sprague-Dawley rat	Inhalation, 50, 100, 150, 200 ppm 6 hr/day, GD 6-20	NOAEL (maternal) = 200 ppm NOAEL (teratogenicity) = 200 ppm NOAEL (fetotoxicity) = 150 ppm. Decreased fetal body weight (females) at 200 ppm.
Isobutyronitrile CAS No. 78-82-0	Sprague-Dawley rat	Inhalation, 50, 100, 200, 300 ppm 6 hr/day, GD 6-20	NOAEL (maternal) = 200 ppm NOAEL (teratogenicity) = 200 ppm NOAEL (fetotoxicity) = 100 ppm. Decreased fetal body weight at 200 and 300 ppm.

Study details are located in the dossiers (Section 5.8.2). GD = gestation day; NOAEL = No observable adverse effect level

Propionitrile has been tested for the ability to cause developmental toxicity at oral concentrations up to 80 mg/kg/day (IRDC, 1981). This study was given a reliability rating of 2 (valid with restrictions), since maternal body weights or weight gains were not analyzed statistically. The authors concluded that the NOAEL for teratogencity was 80 mg/kg, since there was no effect of treatment with up to 80 mg/kg on the incidence of malformations. The summary preparer established a NOAEL for embryotoxicity of 40 mg/kg, since there was a significant increase in the number of early resorptions at 80 mg/kg. The NOAEL for fetotoxicity also was 40 mg/kg, since offspring of dams treated with 80 mg/kg had lower body weights and increased incidences of some skeletal variations compared to controls. This dose appeared to be the NOAEL for maternal toxicity, since the authors stated that dams treated with 80 mg/kg had a slight to moderate reductions in weight gain. However, statistical evidence to support this conclusion was not supplied.

The developmental toxicity of n-butyronitrile has been evaluated in a study similar to OECD test guideline 414, which was given a reliability rating of 1 (valid without restriction) (Stump, 2001b). Groups of pregnant Sprague-Dawley rats were exposed to 50, 100, 150 or 200 ppm n-butyronitrile.

vapor 6 hr/day, from Days 6 – 20 of gestation. On Day 21, all animals were euthanized, and the uterus and contents were weighed. The numbers of viable and non-viable fetuses, resorptions, and implantation sites were also recorded. Each fetus was weighed, sexed and examined for external abnormalities. One half of the fetuses were examined for visceral abnormalities, and the other half was examined for skeletal anomalies. There was no evidence of maternal toxicity (as assessed by body weight changes only) or embryotoxicity, and no effect of treatment on the number of viable fetuses. No visceral or skeletal anomalies were attributed to treatment. The only effect observed in fetuses was reduced body weight of female fetuses from dams treated with 200 ppm. The NOAELs for maternal toxicity and teratogenicity were 200 ppm, and the NOAEL for fetotoxicity was 150 ppm.

The toxicity of isobutyronitrile was examined in a developmental study identical to that described above, with the exception that 50, 100, 200 and 300 ppm were tested (Saillenfait et al., 1993). No visceral or skeletal anomalies were attributed to treatment. The NOAEL for maternal toxicity was 100 ppm, since administration of 200 and 300 ppm caused lethality in a few animals. The NOAEL for fetotoxicity also was 100 ppm, since a reduction in fetal body weight was observed in female offspring from dams treated with 200 ppm, and both sexes at 300 ppm. The NOAEL for teratogenicity was 200 ppm, since 300 ppm caused an increase in embryolethality.

In conclusion, none of the nitriles tested were teratogenic (i.e. caused malformations). Embrolethality occurred after exposure to isobutyronitrile or propionitrile at concentrations that also induced maternal toxicity (300 ppm or 80 mg/kg, respectively). Fetotoxicity (as evidenced by reduced fetal body weights and/or increased incidences of skeletal variants) also was observed in offspring of rats treated with maternally toxic concentrations of all three nitriles. The fetotoxic effects that were observed were nonspecific in nature, and are commonly observed in offspring from dams with lower than normal body weight gains.

3.4.6 Test Plan for Mammalian Toxicity

Adequate acute, genetic and developmental toxicity tests have been performed on all of the category members. Repeated dose and reproductive toxicity studies have been performed with propionitrile. Results of these studies show that the profile of toxicity noted with repeated exposure to propionitrile is consistent with repeated exposure to acutely toxic concentrations that are rapidly eliminated, and that exposure of males and females to concentrations of propionitrile that produce acute symptoms of cyanide toxicity has no effect on fertility. Additional repeated dose or reproductive toxicity testing of the nitriles that have not been tested (n-butyronitrile and isobutyronitrile) is not planned, due to the physical, metabolic and acute toxicological similarities of these materials with propionitrile, and the lack of reproductive toxicity and cumulative repeated dose toxicity with this material.

4. Summary

Physical properties

Measured data are available for melting point, boiling point, vapor pressure and water solubility for all category members. Estimated data for octanol/water partition coefficients are available. Existing data are sufficient to characterize physical property endpoints for these chemicals. As discussed in Section

3.1, the data indicate that the category members behave similarly with respect to physical properties, and serve to support the category approach for these members.

Environmental fate properties

Estimated values are available for all category members with respect to the hydroxyl radical induced photolysis rate constant and atmospheric half-life, Henry's Law Constant, and Fugacity Level III environmental transport parameters. No hydrolysis studies were located for propionitrile, butyronitrile or isobutyronitrile. The theoretical hydrolysis of propionitrile and several other chemicals has been examined by Dr. Lee Wolfe at the USEPA Environmental Research Laboratory in Athens, Georgia. The results of these analyses were published in a report that indicated that propionitrile can hydrolyze slowly. According to a study cited in the Hazardous Substances Data Bank, the chemical hydrolysis of acetonitrile at pH 7 is more than 150,000 yrs. Taken together, these data suggest that hydrolysis of propionitrile, butyronitrile or isobutyronitrile at environmentally relevant pHs will occur too slowly to be a significant means of degradation. Adequate biodegradation tests with all three materials indicate that environmentally relevant concentrations of these materials can degrade over time. Overall, the existing data for environmental fate properties are adequate and demonstrate the similar behaviors of category members.

Aquatic toxicity

Adequate aquatic toxicity data exist for all 3 category members (with the exception of algal toxicity for propionitrile). Available data indicate that the other category members have a similar degree of toxicity toward algae, and that ECOSAR-estimated values for algae are similar. Therefore, it is likely that data for the other nitriles (esp. isobutyronitrile, which has the lowest EC_{50} value) are sufficient to fill the endpoint for propionitrile. The LC/EC_{50} values obtained in the studied species are consistent with the materials being of low level for concern.

Mammalian toxicity

Adequate tests have been performed for all three category members (with the exception of repeated dose and reproductive toxicity). All three nitriles are industrial intermediates with low potential for exposure to the general public. Results of repeated dose and reproductive studies performed with propionitrile will be predictive of those for n-butyronitrile and isobutyronitrile since all three materials have a similar mechanism of action of mammalian toxicity and are virtually identical in structure. No additional testing is necessary.

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